Effect Of Combination Treatment Of Candesartan And Curcumin On Traumatic Brain Injury In Mice

Thesis
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ABSTRACT:

Background: Traumatic brain injury (TBI) is a severe condition and a major cause of death and disability. TBI enhances pro-inflammatory responses and neuronal loss and results in significant disability due to cognitive deficits particularly in attention, learning, memory and locomotor activity. **Aim:** The present experimental study was designed to assess the effect of combination treatment of curcumin and candesartan on TBI in mice. **Methods:** Mice were classified into six groups (Sham, TBI, TBI given the vehicle, TBI treated by curcumin, TBI treated by candesartan and TBI treated by curcumin and candesartan), n=12 each. Mice were anesthetized and then placed under a weight-drop device. The animals were killed by cervical dislocation, brains were rapidly isolated and homogenized. **Results:** TBI group exhibited significant increment in MDA, PGE2, TNF-Alpha, IL1-Beta, caspase -3, NF-κB, iNOS as compared to sham group and these effects were significantly ameliorated by curcumin, candesartan and their combination treatment. Also, short and long term memory, locomotor activity, TAC, SOD, BCL-2 decreased markedly in the TBI group and increased significantly by concurrent treatment with curcumin or candesartan. Furthermore, histopathological examination confirmed these findings. **Conclusion:** Collectively these findings indicate that curcumin and candesartan have potential anti-inflammatory, antiapoptotic and antioxidant effects beside their neuroprotective effect confirmed by the enhanced memory and locomotor activity. Accordingly, curcumin or candesartan might be employed as a therapeutic agent for TBI and the combined drug regimen succeeded in adding better effects than the individual drugs.

Keywords: Curcumin, Candesartan, Traumatic brain injury, Antioxidant, Neuroprotective, Antiapoptotic, Anti-inflammatory.

Contents

List Of Abbreviation

ACE	Angiotensin converting enzyme
AIF	Apoptosis inducing factor
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate
AngI	Angiotensin I
AngII	Angiotensin II
ANOVA	Analysis of variance
AP-1	Activator protein-1
Apaf-1	Apoptotic protease activating factor-1
ARB	Angiotensin receptor blocker
AT1R	Angiotensin type 1 receptor
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BCCAO	Bilateral common carotid artery occlusion
BCl-2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
CAM	Complementary/Alternative Medicine
CaMKII	α-calcium/calmodulin-dependent kinase II
CaN	Calcineurin
Caspases	Cysteinyl aspartate–specific proteases
CBF	Cerebral blood flow

CCI	Controlled cortical impact
CDC	Centers for Disease Control and Prevention
cFPI	Central fluid percussion injury
CNS	Central nervous system
CO	Carbon monoxide
COX	Cyclooxygenase enzyme
CPP	Cerebral perfusion pressure
CREB	Cyclic AMP-response element-binding protein
CSF	Cerebrospinal fluid
CT	Computed tomography
DAI	Diffuse axonal injury
DISC	Death- inducing signaling complex
DNA	Deoxyribonucleic acid
ED	Emergency department
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
ETC	Electron transport chain
FADD	Fas associated death domain
Fas	First apoptosis signal
FasL	First apoptosis signal ligand
FFH	Fall from height
FPI	Fluid percussion injury

g	Gram
GPx	Glutathione peroxidase
GSH	Glutathione
GSSG	Glutathione disulfide
HBOT	Hyperbaric oxygen therapy
H&E	Hematoxylin and eosin
HIV	Human immunodeficiency virus
4-HNE	4-hydroxy-2-nonenal
HO-1	Heme oxygenase-1
HRP	Horseradish peroxidase
IBD	Inflammatory bowel disease
ICAM-1	Intercellular adhesion molecule-1
ICP	Intracranial pressure
IKK	Inhibitory protein Kappa B kinase
IL-10	Interleukin-10
IL-1R1	Interleukin-1 receptor 1
IL-1Racp	IL-1R-accessory protein
IL-1β	Interleukin- 1beta
IL-6	Interleukin-6
IL-8	Interleukin-8
iNOS	Inducible nitric oxide synthase
IRAK	IL-1 receptor-associated kinase

IRI	Ischemia/reperfusion injury
IκB	Inhibitory protein Kappa B
J	Joule
5-LOX	5-lipoxygenase
LPS	Lipopolysaccharide
LTD	long-term depression
LTP	long-term potentiation
MAPK	Mitogen-activated protein kinase
MCs	Mesangial cells
MCAO	Middle cerebral artery occlusion
MDA	Malondialdehyde
MHC	Major histocompatibility complex
MMPs	Matrix metalloproteinases
mPTP	Mitochondrial permeability transition pore
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin
MR	Mineralocorticoid receptor
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MVC	Motor vehicle collision
MWM	Morris water maze
NAC	N-acetylcysteine
NAD	Nicotinamide adenine dinucleotide

NADH	Nicotinamide adenine dinucleotide (reduced form)
NADPH	Nicotinamide adenine dinucleotide phosphate
NBT	Nitroblue tetrazolium
NF-κB	Nuclear factor kappa-B
NIK	Nuclear factor kappa-B -inducing kinase
NLS	Nuclear localization signals
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
OD	Optical density
8-OHdG	8-hydroxy-2′-deoxyguanosine
PCD	Programmed cell death
PEG-SOD	Polyethylene glycol-conjugated superoxide dismutase
PGE-2	Prostaglandin E-2
PLA2	Phospholipase A2
PMs	Phenazine methosulphate
PPARγ	Peroxisome proliferator-activated receptor-gamma
qPCR	Quantitative polymerase chain reaction
RAS	Renin-angiotensin system
RIP	Receptor interacting protein
RNS	Reactive nitrogen species

ROIs	Reactive oxygen intermediates
ROS	Reactive oxygen species
RT-PCR	Reverse transcription-polymerase chain reaction
SEM	Standard error of mean
SOD	Superoxide dismutase
STZ	Streptozotocin
TAC	Total antioxidant capacity
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
TBI	Traumatic brain injury
TCA	Trichloroacetic acid
TLR	Toll-like receptor
TMB	Tetra methyl benzidine
TNFR1	Tumor necrosis factor receptor 1
TNF-α	Tumor necrotic factor- alpha
TRADD	Tumor necrosis factor receptor associated death domain
TRAF 2	TNFR- associated factor 2
UPS	Ubiquitin proteasome system
VCAM-1	Vascular adhesion molecule-1
VSM	Vascular smooth muscle
WDI	Weight drop injury

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